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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,400	11/23/2005	Patrick Gallois	264231US0PCT	6825

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EXAMINER	
ZHENG, LI	

ART UNIT	PAPER NUMBER
1638	

NOTIFICATION DATE	DELIVERY MODE
08/24/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/519,400	GALLOIS ET AL.	
	Examiner	Art Unit	
	Li Zheng	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *8-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☒ Claim(s) *4-7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/11/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-29 are pending.

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 1-7, and SEQ ID NO: 10 in the reply filed on 6/7/2007 is acknowledged. However, it is noted that restriction requirement between SEQ ID NO: 1-10 is not considered as a species election. Applicants traverse the restriction requirements between Group I-IX.

Applicants contend that the Office has not provided any indication that the contents of the claims interpreted in light of the description was considered in making the assertion of a lack of unity and therefore has not met the burden necessary to support the assertion (response, page 3, 2nd paragraph).

The Office contends that while the claim should be interpreted in light of the specification, reading the limitation not recited into the claim is not proper. As discussed in the previous office action, the technical feature linking those invention groups is a protein substantially homologous to SEQ ID NO: 10, which is anticipated by Broekaert et al, given the undefined recitation "substantially homologous".

Claims 8-29 are drawn to non-elected subject matter and are therefore withdrawn from consideration.

Claims 1-7 including SEQ ID NO: 10 are examined on the merits.

Claim Objections

3. Claims 2 and 3 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The instant claim 1 on which claim 2 is dependent has a narrower scope than claim 2. Similarly, the instant claim 2 on which claim 3 is dependent has a narrower scope than claim 3.

4. Claims 4-7 are objected to under 37 CFR 1.75(c) as being in improper form because multiple dependent claim 4 is dependent on another multiple dependent claim 3. See MPEP § 608.01(n). Accordingly, the claims 4-7 have not been further treated on the merits.

5. Claims 1-7 are objected to because it contains non-elected subjected matter. As discussed above, restriction requirement between SEQ ID NO: 1-10 is not considered as a species election. Correction is requested.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 1-3 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims are drawn towards an isolated, natural, or synthetic polypeptide (emphasis added).

As written, claim 1 reads on a natural polypeptide *per se* which is found in nature and thus, is unpatentable to applicant. The polypeptide, as claimed, has the same characteristics as those found naturally in the genome or as cellular precursors thereof and therefore does not constitute patentable subject matter. See *American Wood v. Fiber Disintegrating Co.*, 90 U.S. 566 (1974), *American Fruit Growers v. Brodgex Co.*, 283 U.S. 2 (1931), *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 33 U.S. 127 (1948), *Diamond v. Chakrabarty*, 206 USPQ 193 (1980). It is suggested that claim 1 be amended by deleting the term "natural" to identify a product that is not found in nature.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "R1 and R2" in line 4. There is insufficient antecedent basis for this limitation in the claim.

In claim 3, the recitation, "substantially", renders the claim indefinite. The term is a relative term with no definite meaning. It is unclear what is considered to be substantially homologous to SEQ ID NO: 10. The metes and bounds are not clear.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an isolated, natural, or synthetic polypeptide comprising SEQ ID NO: 10 or a polypeptide having substantial homology to SEQ ID NO: 10.

The office interprets the claimed genus to encompass any polypeptide having any sequence homology to SEQ ID NO: 10.

The specification discloses three isolated or synthetic polypeptides, Pep25aa, Pep2S and Pep1S, comprise SEQ ID NO: 10, in which Xaa represents a cysteine or a serine (specification, Figure 5A). The specification teaches that while Pep25aa and Pep2S have cytotoxic activities, Pep1S no longer has cytotoxic activity (specification, Figure 5A and page 48, lines 1-3).

The Applicants do not identify all essential regions of the protein of SEQ ID NO:10, nor do Applicants describe any polypeptide that is substantially homologous to SEQ ID NO:10. The specification only correlates Pep25aa and Pep2S with the cytotoxic activity.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In summary, the court stated that a written description of an invention requires a precise definition, one that defines the structural features of the chemical genus that distinguishes it from other chemical structures. A definition by function does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. The court goes on to say, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicants fail to describe a representative number of the proteins falling within the scope of the claimed genus of polypeptides which comprise polypeptides having substantial homology to SEQ ID NO: 10. Applicants only describe two of the polypeptides, Pep25aa and Pep2S, that have the cytotoxic activity. Furthermore, Applicants fail to describe structural features common to members of the claimed genus of polypeptides. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for the protein of SEQ ID NO: 10, it remains unclear what features identify a protein of SEQ ID NO: 10. Since said genus has not been described by specific structural features, the specification fails to provide an adequate written description to support the breath of the claims.

Scope of Enablement

9. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Pep25aa and Pep2S, does not reasonably provide enablement for any other polypeptide having SEQ ID NO: 10 or any polypeptide having substantial homology to SEQ ID NO: 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir.

1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are drawn to an isolated, natural or synthetic polypeptide comprising SEQ ID NO: 10 or a polypeptide having substantial homology to SEQ ID NO: 10.

The office interprets the claimed genus to encompass any polypeptide having any sequence homology to SEQ ID NO: 10 because of the 112 2nd rejection for "substantially" as discussed above.

The specification discloses three isolated or synthetic polypeptides, Pep25aa, Pep2S and Pep1S comprising SEQ ID NO: 10, in which Xaa represents a cysteine or a serine (specification, Figure 5A). The specification teaches that while Pep25aa and Pep2S have cytotoxic activities, Pep1S no longer has cytotoxic activity (specification, Figure 5A and page 48, lines 1-3).

The specification also fails to provide guidance in terms of how to make modifications to the SEQ ID NO: 10 to generate the claimed genus of variants that retain its cytotoxic activity.

Falcon-Perez JM et al. (1999, *J Biol Chem.* 274:23584-90) teach that when twenty-two single amino acid substitutions or deletions were introduced into the nucleotide binding domains, the proposed regulatory domain, and the fourth

cytoplasmic loop of the yeast cadmium factor (Ycf1p) vacuolar protein by site-directed mutagenesis, two conserved amino acid residues, Glu (709) and Asp (821), were found to be unnecessary for Ycf1p biogenesis and function.

The state of art also teaches that making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al. (1988, Mol. Cell. Biol. 8:1247-1252) teach that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). All these mutated proteins would have at least 95% identity to the original protein.

Guo et al. (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2).

Therefore, the instant specification fails to provide guidance for which amino acids of SEQ ID NO: 10 can be altered, the type of alteration, and which amino acids must not be changed, to maintain cytotoxic activity of the e protein. The specification

also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional cytotoxic polypeptide.

Further, even for the polypeptides comprising SEQ ID NO: 10, the specification clearly teaches that only while Pep25aa and Pep2S have cytotoxic activities, Pep1S no longer has cytotoxic activity (specification, Figure 5A and page 48, lines 1-3). Therefore Pep1S comprising SEQ ID NO: 10 is not enabled

Without further guidance, undue experimentation would be required for a person skilled in the art to design 20^{25} variants of a polypeptide with 25 residues, synthesize the protein and test their cytotoxic activity against plant pathogens. See *Genentech Inc. v. Novo Nordisk,* A/S (CA FC) 42 USPQ2d 1001 (Fed. Cir. 1997), which teaches that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention.

Therefore, given the claim breadth, lack of further guidance and additional working example, unpredictability of the art, undue experimentation would be required for a person skilled in the art to practice the invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Li Zheng whose telephone number is 571-272-8031. The examiner can normally be reached on Monday through Friday 9:00 AM - 5:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on 571-272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

STUART F BAUM, PH.I
PRIMARY EXAMINER